III. REMARKS

Applicants respectfully request reconsideration of this application in view of the following remarks.

1. Status of the Claims

Claims 1-10 and 14-17 are pending in this application. Of these claims, Claims 14-17 have been withdrawn from consideration. Claims 11-13, 18 and 19 have been previously cancelled. Accordingly, Claims 1-10 are currently pending for examination on the merits.

2. Requirement for Restriction Under 35 U.S.C. §121

Applicants acknowledge that the requirement for restriction imposed on the pending claims under 35 U.S.C. §121 has been made final. Accordingly, Applicants respectfully requested rejoinder of any product claims that are found to be allowable with any method of use claims which depend from or otherwise include all the limitations of the allowed product claims as provided for in MPEP §821.04 and *In re Ochiai* 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995).

3. Rejections Under 35 U.S.C. §103

Claims 1, 2, 5, 7 and 8 have been rejected under 35 U.S.C. §103(a) as being unpatentable over EP 463 653 A1, to Roberto et al., in view of U.S. Patent No. 4,639,433, to Hunt et al.; EP 094 157 A1, to Hirai et al.; U.S. Patent No. 6,048,845, to Rubinfeld; and Pea et al., *J. Antimicrob. Chemother.* (2000) **45**, 329-335. Additionally, Claims 3, 4, 6, 9 and 10 have been rejected under 35 U.S.C. 103(a) as being unpatentable over various combinations of the above documents as set forth in the Final Office Action. The Examiner also discusses Uekama et al., *J. Pharm. Pharmacol.* (1993) **45**, 745-747 in the Final Office Action, although no official rejection appears to be based on this document. For the following reasons, the above rejections are

respectfully traversed.

The presently claimed subject matter is directed to a pharmaceutical composition comprising (a) a cyclodextrin and (b) a lipidated glycopeptide antibiotic or a pharmaceutically acceptable salt thereof; and to methods of using such pharmaceutical compositions. Surprisingly, Applicants have discovered that combining a cyclodextrin with a lipidated glycopeptide antibiotic reduces or eliminates several undesired properties of the lipidated glycopeptide antibiotic, including reducing nephrotoxicity and excessive tissue accumulation of the lipidated glycopeptide antibiotic (see, for example, page 1, lines 19 to 23 of Applicants specification).

The Examiner has taken the position that the cited references provide one skilled in the art with the motivation to combine a cyclodextrin with a lipidated glycopeptide antibiotic. Specifically, the Examiner has indicated that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references because (a) Roberto et al. teach a pharmaceutical composition comprising a cyclodextrin and peptide antibiotic, (b) Hunt et al. teach the type of the peptide antibiotic is a lipidated glyco-peptide antibiotic, and (c) Hirai et al. teach a pharmaceutical composition comprising cyclodextrin and the bioactive component, e.g., peptide antibiotic, the weight percent of the cyclodextrin and freeze-dried power [sic] form of the composition. When combined, there would be the following advantages: (i) high level of bioavailability (see page 15, line 25), (ii) improve drug efficacy in view of biological half-life of the administrated drug (see page 18, lines 30-34), (iii) low cyctotoxicity (see page 18, lines 34-38) and (iv) permutable repeated dose regimens (see page 18, lines 21-38), as taught by Hirai et al. Cyclodextrin-formulated pharmaceutical compositions has an especial [sic] benefit for formulating cyctotoxic drug, e.g., antibiotic such as glycopeptide antibiotic (e.g., bleomycins) (see abstract, column 5, lines 33-48, column 6, lines 6-48, and column 11, lines 48-53 of the Rubinfeld et al. patent). The benefit taught by Rubinfeld et al. is to reduce/eliminate cytotoxic agent (e.g. cytotoxic antibiotic) caused irritation or ulceration when administering the cytotoxic antibiotic (see column 5, lines 37-43).
>
> Moreover, it has been known in the prior art of record that cyclodextrin formulated in the pharmaceutical composition reduces the cytotoxicity of the

composition comprising toxic antibiotic (see the Roberto et al. teaching , especially abstract), which would be noticeably advantageous to the glyco-peptide antibiotics (e.g. vancomycin) which have undesirable nephrotoxicity (see the Pea et al. reference, at page 330, the left column, lines 3-4), and to aminoglycoside antibiotics (e.g. gentamicin) in that cyclodextrin has a protective effect against the antibiotic-induced nephrotoxicity in a mammal (see Uekama, K. et al. (1993) *J. Pharm. Pharmacol.* 45, 745-747).

Given the above motivation, one of ordinary skill in the art would have combined the above referenced teachings to develop the pharmaceutical composition comprising the potential toxic glyco-peptide antibiotic and the cyclodextrin for achieving high pharmaceutical efficacy and lower cytotoxicity of the antibiotics. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made. (Final Office Action, pp. 7-8).

Assuming for the sake of argument that the cited references provide sufficient motivation to establish a *prima facie* case of obviousness, it is well established that a *prima facie* case of obviousness can be rebutted by evidence showing that the claimed subject matter possesses a superior or unexpected property.

In the present case, Applicants have presented data in the specification demonstrating that the claimed composition provides both reduced tissue accumulation and reduced nephrotoxicity. Specifically, Applicants demonstrate in Example 6 (beginning on page 53, line 20) that a cyclodextrin dramatically reduces tissue accumulation (Table 1 on page 54) and nephrotoxicity (Table 2 on page 55) for a lipidated glycopeptide antibiotic. For the Examiner's convenience, Tables 1 and 2 are reproduced herein as follows:

TABLE 1

Tissue Distribution and Urinary Recovery for Compound A in Various Formulations Following Intravenous Infusion to Female Rats at a dose of 50 mg/kg. (Values are Mean (SD))

Compound (Formulation)	Serum Conc. (μg/mL)	% Recovered (as unchanged parent)		
		Urine	Liver	Kidney
Compound A (25% CD)	0.86 (0.19)	90.91 (8.39)	1.90 (0.32)	0.62 (0.12)
Compound A (5% CD)	1.66 (0.33)	40.51 (18.57)	4.89 (0.81)	2.08 (0.43)
Compound A (1% CD)	17.1 (12.1)	17.45 (6.92)	8.47 (0.46)	5.68 (2.49)
Compound A (D5W)	59.8 (27.1)	12.61 (4.60)	14.19 (3.41)	17.82 (4.94)

CD = hydroxypropyl-β-cyclodextrin

D5W = aqueous 5% dextrose solution

As shown in Table 1, urinary recovery of Compound A was significantly higher in formulations contain a cyclodextrin; and liver and kidney accumulation were significantly lower in such formulations. For example, urinary recovery of the lipidated glycopeptide antibiotic went from 12.61% without cyclodextrin to 90.91% with a 25 weight percent cyclcodextrin formulation. Similarly, liver accumulation went from 14.19% without cyclodextrin to 1.90% with a 25 weight percent cyclodextrin formulation.

TABLE 2

Effects of Compound A Formulation on Serum Renal Chemistry

Compound	Formulation	BUN (mg/dL)	Creatinine (mg/dL)
Vehicle	25% (w/v) CD	14 ± 1	0.26 ± 0.06
Compound A	25% (w/v) CD	13 ± 2	0.26 ± 0.02
Vehicle	5% (w/v) CD	10 ± 1	0.21 ± 0.01
Compound A	5% (w/v) CD	18 ± 5	0.31 ± 0.07
Vehicle	1% (w/v) CD	13 ± 2	0.24 ± 0.01
Compound A	1% (w/v) CD	26 ± 5	0.34 ± 0.08
Vehicle	D5W	12 ± 2	0.28 ± 0.02
Compound A	D5W	67 ± 2	0.72 ± 0.08

CD = hydroxypropyl-β-cyclodextrin

D5W = aqueous 5% dextrose solution

The results in Table 2 show that the formulations containing cyclodextrin had significantly less nephrotoxicity compared to formulations without cyclodextrin. For example, BUN levels decreased from 67 ± 2 mg/mL to 13 ± 2 mg/mL (equivalent to vehicle alone) when the lipidated glycopeptide was formulated with 25 weight percent glycopeptide.

Accordingly, the data in Tables 1 and 2 clearly demonstrate that cyclodextrins have surprising and unexpected effects on the tissue accumulation and nephrotoxicity of lipidated glycopeptide antibiotics.

In contrast, the cited references do not teach or suggest that pharmaceutical compositions comprising a cyclodextrin and a lipidated glycopeptide antibiotic would have either reduced tissue accumulation or reduced nephrotoxicity compared to formulations without the

cyclodextrin. First, none of the cited references even discuss the problem of tissue accumulation of lipidated glycopeptide antibiotics – let alone suggest a solution to this problem.

In this regard, the Examiner has indicated "the property of the cyclodextrin...reducing antibiotic renal accumulation has been demonstrated by Uekama et al. (see abstract, Figures 2-3 and pages 746-747)." Final Office Action at page 9 (emphasis in original). However, Uekama et al. teaches exactly the opposite! More specifically, Uekama et al. teach the following:

> ...the effect of cyclodextrin sulphates on the renal accumulation of the drug was examined. β-Cyclodextrin sulphate, when given 6 h after gentamicin administration, ***did not reduce the total amount of the drug stored in the kidney*** for up to nine days. (Fig. 3). Uekama et al. beginning at bottom of page 746 (emphasis added).

With regard to teachings of Uekama et al, Applicants first note that gentamicin is not a lipidated glycopeptide and therefore, the teachings of Uekama et al. are not necessarily relevant to lipidated glycopeptides. However, to the extent that the Uekama et al. document is applicable, it clearly teaches that cyclodextrin sulfate does not effect accumulation of the antibiotic gentamicin in the kidney.

Accordingly, the cited reference are either silent with regard to tissue accumulation or, in the case of Uekama et al., they teach that a cyclodextrin does not effect tissue accumulation of an antibiotic. Therefore, in view of the teachings of the cited references, Applicants discovery that presently claimed pharmaceutical compositions provide reduced tissue accumulation of a lipidated glycopeptide antibiotic is clearly surprising and unexpected. This surprising and unexpected result, which is neither taught nor suggested by the cited references, is sufficient to rebut a *prima facie* case of obviousness. Therefore, based on these data alone, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

In addition, however, the cited references do not teach or suggest that pharmaceutical compositions comprising a cyclodextrin and a lipidated glycopeptide antibiotic would have

reduced nephrotoxicity compared to formulations without the cyclodextrin.

For example, the Rubinfeld reference discloses that "extravasation-associated ulceration" and related irritation caused by cytotoxic compounds can prevented by using a cyclodextrin (see, for example, column 5, lines 18-42). Thus, the Rubinfeld reference is not concerned with nor does it suggest a solution to the problem of nephrotoxicity caused by lipidated glycopeptide antibiotics.

The Hirai et al. reference is directed to pharmaceutical compositions containing a hydrophilic drug and a cyclodextrin, and the administration of such pharmaceutical compositions through, for example, the nasal cavity (see, for example, page 2, lines 01-08). In this regard, Harai et al. teach that cyclodextrin itself has low toxicity (page 18, lines 34-38). However, as with the Rubinfeld reference, the Harai et al. reference is not concerned with nor does it suggest a solution to the problem of nephrotoxicity caused by lipidated glycopeptide antibiotics.

Additionally, the Hunt et al. reference merely teaches a particular type of lipidated glycopeptide antibiotic but does not teach or suggest the problem of nephrotoxicity of such compounds or a solution to the problem. Similarly, the Pea et al. reference identifies the problem of nephrotoxicity caused by a glycopeptide antibiotic (i.e., vancomycin) but suggests only the solution of measuring serum concentrations of vancomycin to avoid nephrotoxicity (see page 330, left column, lines 1-5).

The Uekama et al. reference teaches that cyclodextrin sulfates protected the rat against gentamicin-induced nephrotoxicity. However, as previous mentioned, gentamicin is not a lipidated glycopeptide antibiotic. Specifically, gentamicin has no lipid moiety and no glycopeptide moiety. Therefore, one skilled in the art would not have a reasonable expectation of success based on the teachings of Uekama et al. that a cyclodextrin would reduce the observed tissue accumulation of a lipidated glycopeptide.

Finally, the Roberto et al. reference discloses pharmaceutical compositions comprising a drug, an enhancer of absorption at a mucosal surface and a cyclodextrin (see, for example,

column 3, lines 16-23). This reference teaches that when an absorption enhancer is used in combination with a cyclodextrin, the undesirable side effects due to the enchancer (such as lipid disruption) may be reduced (see column 3, lines 09-15).

The Roberto et al. reference does not disclose lipidated glycopeptide antibiotics nor does it disclose the problem of nephrotoxicity caused by lipidated glycopeptide antibiotics. Accordingly, Applicants' discovery of the dramatic reduction in nephrotoxicity is certainly surprising and unexpected in view of this reference.

Moreover, the Roberto et al. reference actually reports that rat nasal tissue exposed to 2-hydroxypropyl-β-cyclodextrin showed some signs of interaction between the epithelium and the dose (see column 17, lines 05-12). More specifically, Roberto et al. report:

> On close inspection, the epithelium on the dosed side appeared to be more "disordered" than the control tissue with the line of cilial basal bodies at the luminal surface interrupted at intervals. The nuclei of the epithelial cells on the dosed side tended to be smaller and more irregularly shaped than the large rounded nuclei in the untreated epithelium, particularly over the central septum areas. Also dosed nuclei were stained more densely obscuring intranuclear detail and tended to be more closely packed at the basal membrane. These observations suggest some interaction between dose and tissue, possibly in the early stages. Column 17, lines 22-35.

Accordingly, Applicants' discovery of reduced nephrotoxicity is even more unexpected and surprising in view of this teaching by Roberto et al. that cyclodextrins effect epithelial cells.

Thus, in summary, none of the cited references either alone or when combined with each other teach or suggest that pharmaceutical compositions comprising a cyclodextrin and a lipidated glycopeptide antibiotic would have reduced tissue accumulation and reduced nephrotoxicity compared to formulations without the cyclodextrin. Accordingly, Applicants' data are surprising and unexpected in view of the cited references and as a result, such data are sufficient to rebut a *prima facie* case of obviousness. Therefore, Applicants respectfully request

that the rejection under 35 U.S.C. §103(a) be withdrawn.

4. Information Disclosure Statements

In the Final Office Action, the Examiner indicated that the Information Disclosure Statement (IDS) filed on November 8, 2001 is missing and therefore, the references listed on this IDS will not be listed on any patent issuing from this application.

In response, Applicants note that the Examiner has returned to Applicants initialed PTO-1449s for the IDS's submitted on November 8, 2001; February 26, 2002; and April 30, 2002. Copies of these initialed PTO-1449s are enclosed herewith.

Since the documents submitted by Applicants in these IDSs have clearly been considered by the Examiner (as evidenced by the initialed PTO-1449s), Applicants respectfully request that these documents be listed on any patent that issues from this application. The Examiner is respectfully requested to contact the undersigned attorney for Applicants should any additional information be required regarding these documents.

5. Telephonic Interview

Applicants requested a telephonic interview for this application on May 3, 2004. In preparing for the interview, the Examiner kindly reviewed the file and subsequently indicated that he would most likely withdraw the rejections and allow this application. Accordingly, the interview was canceled. Should the Examiner determine upon further review that there are any pending issues, Applicants would appreciate the opportunity to conduct a telephonic interview to discuss such issues.

Consideration of the above remarks is respectfully requested. Applicants believe this application is in condition for allowance and a notice to that effect is respectfully requested. Should there be any questions concerning this response, the Examiner is requested to telephone the undersigned attorney at (650) 808-6406.

Respectfully submitted,

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